REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

The foregoing amendments are submitted concurrently with the filing of an RCE.

I. Amendments

Claims 2, 6, 9-12, 14, 17-20, 63-82, and 91 are cancelled without prejudice, and new claims 92-117 are added.

The main points of the amendments are as follows.

(i) In claims 1, 5, 13 and 89 a nanoparticle suspension is excluded, and the upper limit of the mean particle size of the micronized AS-3201 is changed to "10 μm" from "20 μm". This upper limit of the mean particle size is supported in the original claim 2. Support for exclusion of nanoparticle suspensions is submitted to be inherent from the specification and to help to distinguish the invention from the art.

(ii) In claims 4 and 8, and the new claims 92, etc., the lower limit of the mean particle size is specified to "about 1.2 μm" instead of "1 μm". Support for the lower limit of mean particle size of "about 1.2 μm" is submitted to be inherent, based upon the teachings of the specification of mean particle size of "most preferably in the range of about 0.5 mm to about 3 mm" (page 4, lines 2-5 of the specification and "about 1.5 mm" (page 10, lines 18-22 of the specification).

As is explained below, in Declaration D, it is shown that tablets prepared from AS-3201 particles having a mean particle size of 1.18 μm at minimum showed an excellent dissolution rate. Moreover, it is shown in Example 1 on page 10 of the original description micronized particles having a mean particle size of about 1.5 μm, which is approximately equal to 1.2 μm, and hence any person skilled in the art would readily understood that the lower limit of "about 1.2 μm" would be implicitly and inherently taught by the original specification.

(iii) In the new claims 93, etc. the lower limit of "1.5 μm" is supported by Example 1 of the original specification.

(iv) In claim 89, the "acidity more potent than that of AS-3201" is specified to "a pKa of less than about 5.6" in view of the objection by the Examiner, which is supported by the original specification, page 6, lines 15-18.

(v) In new claims 97, etc., the solid dosage form is specified to be tablets, capsules, granules or powder, which is supported by the original specification, page 5, lines 2-5.

II. Filing of new Declarations (Declaration C, D and E)

The Applicants wishes to show some experimental data in the form of a declaration. At this time, the following three declarations are submitted.

(1) Declaration C: It is shown that AS-3201 particles do not match the Noyes-Whitney Law based on the new findings by these experiments.

(2) Declaration D: It is shown that AS-3201 particles pulverized by a Jet Mill had a mean particle size of 1.36 μm (in average), 1.18 μm (at minimum), and 1.62 μm (at maximum), and further that the tablets used in the clinical studies in the U.S.A. (mean particle size of AS-3201: 1.18μm) had an excellent dissolution rate.

(3) Declaration E: It is shown that AS-3201 alone is stable but when it contacts common pharmaceutical excipients, it becomes unstable and further that a pharmaceutical composition of AS-3201 containing an acid is more stable than a pharmaceutical composition containing no acid.

III. Comments on the Office Action

A. Re: Claim Rejections -35USC§112

It is believed that all rejections and objections will be obviated by the foregoing amendments.

B. Re: Rejections of claims 1-20 and 63-82 under 35 USC 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Muller et al (5,858,410)

With respect to the primary reference, Negoro et al., the Applicant has already explained how the present invention can be distinguished from Negoro et al., and the Applicant believes that such distinctions are clear. However, the Examiner still adheres to the position that the secondary reference, Muller et al., disclose microparticles overlapping with the micronized particles of the present invention and thus that the present invention is unpatentable over the combination of Negoro et al. and Muller et al.

Accordingly, the Applicant would like to explain in more detail how the disclosure of Muller et al. is distinguished from the present invention.

[1]-1. Disclosure of Muller et al. relating to Noyes-Whitney law

The Examiner adheres to the position that the dissolution phenomenon of nanoparticles disclosed in Muller et al (the Examiner mentioned this phenomenon as a"65% dissolution rate") matches the Noyes-Whitney law, while the Applicant argued that this phenomenon matches the Ostwald-Freundlich equation as disclosed in col.5, line 66 to col. 6, line 7 of Muller et al. but is clearly distinguished from "dissolution phenomenon" which matches the Noyes-Whitney law.

The Applicant respectfully submits that the position of the Examiner is in error, caused by the following misleading description of Muller et al., col.1, lines 44-51:

"1. The dissolution rate increases as the particle surface area increases in accordance with the Noyes-Whitney law. As a result, the rate of flooding of active compounds increase, and the maximum plasma level is reached faster (e.g. oral or i.v. administration of a nanosuspension). The preparation of nanosuspensions is therefore of interest for all substances with which the dissolution rate is the determining factor for the bioavailability."

Firstly, the formula of Noyes-Whitney law does never include any factor as to bioavailability, and there is no direct correlation between an increase of surface area and an improvement of bioavailability.

Secondly, the term "bioavailability" is used only once in Muller et al. and there is no specific description supporting it. In addition, the results in Example 8 and Fig. 9 of Muller et al. conforms to the Ostwald-Freundlich equation, and Muller et al. never prove that it shows a "faster dissolution rate" conformable to the Noyes-Whitney law.

Thirdly, the above statement from Muller et al. is merely mentioned in general terms as to nanoparticle suspensions, and is not relevant to a solid dosage form including microparticles.

Fourthly, according to the decision of Board of Patent Appeals in the USPTO, it is prohibited to connect unduly the disclosure of Muller et al. to the Noyes-Whitney law.

That is, according to the following opinion shown with respect to the relation of pulverization and dissolution rate in the case of Arbuthnot et al., of which it will be explained in more detail hereinafter:

"Although prior art of record taught that size reduction in general is prima-facie obvious approach to increase dissolution rate but the selection of a particular range of particle size are more often solved empirically rather than through theoretical route."

Thus, it is prohibited to deny unobviousness through a theoretical route, i.e. through the teaching of the Noyes-Whitney law.

Thus, it is respectfully submitted that the Examiner misunderstands the Noyes-Whitney law, and on the basis of such misunderstanding, the Examiner has misevaluated the disclosure of Muller et al., and wrongly connected the Noyes-Whitney law with bioavailability. Accordingly, the rejection is incorrect and should be withdrawn.

[1]-1-1. Noyes-Whitney law is not adoptable to every compound

The Applicant has repeatedly pointed out that the Noyes-Whitney law is never adoptable to every compound, for example, in page 6 of the Applicant's response dated April 4, 2003 as well as in page 28 of the Response on Sep. 9, 2004. The literature referred to therein is the following one:

> "Design and Evaluation of Peroral Pharmaceutical Preparation (in Japanese)" edited by Mitsuru Hashida, Yakugyou Jihosya, Feb. 10, 1955, pp81-84, 168-171 (cited in the International Search Report of the original PCT/JP98/04658) thereof (which was submitted as Supplemental Information Disclosure Statement on Sep. 26, 2000)"

The Examiner agreed with this position in the outstanding Final Office Action, page 9, lines 6-8 as follows:

"With regard to the assertion that the Noyes-Whitney law does not apply to every compound, the examiner does not assert that this law applies to every compound known.

The examiner merely notes that this is a general theory that is starting point to experiment."

The above Examiner's comments will be reasonable in view of the position taken by Board of Patent Appeals where it is prohibited to deny unobviousness through theoretical route, in other words, through the teaching of Noyes-Whitney law.

[1]-1-2. "Specific extraordinary circumstance" which AS-3201 is not conformable to Noyes-Whitney law

It is mentioned in "Design and Evaluation of Peroral Pharmaceutical Preparation (in Japanese pp 168-171)" (English translation, page 1, lines 5-4 from the bottom, submitted as IDS) as follows:

"In particular, hydrophobic drugs are very apt to flocculate."

Thus, this prior art teaches that hydrophobic drugs flocculate by pulverization and is not conformable to Noyes-Whitney law.

Then, the question is raised whether AS-3201 is a hydrophobic drug. It has already been proved by the experiment shown in Mr. Sanjoba's Declaration submitted on September 9, 2004. Thus, since AS-3201 is a hydrophobic drug, there is a "specific extraordinary circumstance" that it will be expected that AS-3201 flocculates and hence is not conformable to Noyes-Whitney law.

The above has already been argued in the Applicant's Response of Sep. 9, 2004, page 29, but nevertheless, the Examiner still points out in the outstanding Final Office Action, page 2, last paragraph as follows:

"Firstly, it is unclear the purpose of the Rule 132 declaration, in terms of unexpected results. The examiner notes that the Rule 132 declaration of 9/9/04 does not specify the particle size, which is the main issue in the following rejections. The Rule 132 declaration is merely demonstrating the solubility of AS-3201 in various solvents, which is not claimed. Therefore, the Rule 132 declaration is insufficient to overcome the following rejections."

Thus, the purpose of the Declaration is to show that AS-3201 is a hydrophobic drug, so that it will be expected that it flocculates.

Now, this proposition has been experimentally proved as is shown in Ohashi's Declaration (C), Experiment 1(3) and Experiment 4(2). Therein, it is shown that AS-3201 had a large electrical charge and flocculated. Thus, it was experimentally proved that AS-3201 is not conformable to the Noyes-Whitney law (not a mere presumption).

[1]-1-3. Comparison of dissolution properties between tablets containing nanoparticles and tablets containing microparticles

The Examiner points out in the outstanding Office Action, page 9, lines 8-10 as follows:

"If this theory (i.e. Noyes-Whitney law) does not apply to the instant compound, then the applicant must show this in a Rule 132 declaration since the USPTO is not capable of performing such tests"

As is shown in Mr. Ohashi's Declaration (C), the following facts have experimentally been found:

(a) The experiment failed to prepare nanoparticles by the dry pulverization method [Experiment 1] because AS-3201 had a large electrical charge and flocculated. From this fact, it is understood that it is difficult to obtain nanoparticles of AS-3201 by dry pulverization method.

(b) In order to prepare nanoparticles by the wet pulverization method, it was tried to prepare a suspension of microparticles of AS-3201, but AS-3201 microparticles alone could not be suspended in water [Experiment 2].

(c) Mr. Ohashi found that AS-3201 microparticles could be suspended in water in the presence of hydroxypropylcellulose (= HPC). Accordingly, he prepared a suspension containing AS-3201 (mean particle size, 1.36 μm) and HPC (hereinafter, optionally referred to as "pre-pulverization suspension), and then, the suspension was subjected to wet pulverization 20 times with DeBEE homogenizer, and thereby he has succeeded to obtain a suspension containing AS-3201 nanoparticles (mean particle size: 630 nm) (hereinafter, optionally referred to as "post-pulverization suspension) [Experiment 3].

[Note]: The principle of pulverization with DeBEE homogenizer is the same as the pulverizer mentioned in Muller et al.

(d) Studying to take out powdery AS-3201 from a suspension containing AS-3201, Mr. Ohashi obtained the following new findings.

(i) In order to obtain powdery nanoparticles of AS-3201, the post-pulverization suspension (0.630 μm) as mentioned in the above (c) subjected to vacuum drying, and a hard agglomerate was obtained and the agglomerate was crushed in a mortar [Experiment 4(1)]. The particles thus obtained were neither nanoparticles nor microparticles (= the microparticles of the present invention).

(ii) Further in order to obtain powdery nanoparticles of AS-3201, the post-pulverization suspension (0.630 μm) as mentioned in the above (c) subjected to freeze drying, and there was obtained the powdery product having mean particle size of 41.6 μm) [Experiment 4(2)(i)]. The particles thus obtained were neither nanoparticles nor microparticles (= the microparticles of the present invention).

(iii) In order to obtain the powder as a control sample, microparticle of AS-3201, the pre-pulverization suspension (1.36 μm) as mentioned in the above (c) subjected to freeze drying, and there was obtained the powdery product having mean particle size of 8.2 μm [Experiment 4(2)(ii)].

(iv) From the above results in (ii) and (iii), when a suspension containing nanoparticles or microparticles was freeze-dried, the former has larger mean particle size than that of the latter. Accordingly, it was proved that the smaller the mean particle size of AS-3201, the larger the flocculate force of the particles [Experiment 4(2)(i) and (ii)].

(e) Using two kinds of suspension containing AS-3201, two kinds of tablets were prepared by spraying method, and the dissolution rate of the tablets was measured. As a result, both tablets showed substantially the same dissolution rate as shown in the following table (cf. Experiments 5 and 6).

Sample	Sprayed Suspension	Dissolution Rate (%)	
		After 15 minutes	After 30minutes
Tablet A	Suspension of nano-particles (0.630μm)	97.3	99.5
Tablet B	Suspension of micro-particles (1.36μm)	95.3	99.5

As the Applicant has repeatedly argued, the smaller the particles of AS-3201, the more they flocculate, and hence AS-3201 is not conformable to Noyes-Whitney law. Thus, it has been experimentally confirmed that the Applicant's argument is correct as shown by the Ohashi's Declaration (C).

The above fact is again explained. Said Tablets A and B were prepared by Spraying Method, and as is shown in Ohashi's Declaration (C), any powdery nanoparticles could not be obtained from the suspension containing nanoparticles, and then, it was tried to prepare tablets directly from the suspension. According to this method, the suspension containing AS-3201 was sprayed on pharmaceutical excipients and then the resulting granules were tableted.

Since it is very difficult to measure the particle size of AS-3201 contained in the tablets, and hence if it is assumed that the particle size did not change during spraying step, the AS-3201 particles contained in Tablet A should have a mean particle size of 0.630 μm and that in Tablet B should have a mean particle size of 1.36 μm. With this assumption, it was evaluated the dissolution properties of AS-3201 from these tablets along with Noyes-Whitney law. As a result, it was calculated that Tablet A (0.630 μm) had a dissolution rate of about 4.7 times larger than that of Table B 1.36 μm) [$= (1.36/0.63)^2$] . Contrary to thus assumption, as is proved by experiments, both tablets showed substantially the same dissolution rate.

Thus, it was clearly confirmed that AS-3201 does not follow the Noyes-Whitney law.

Please also note that the results of Mr. Ohashi's Declaration (C) is believed to satisfy the following request by the Examiner as mentioned in the outstanding Final Office Action, page 9, lines 10-13:

> "The examiner notes that the applicant has still not compared a nanometer range, i.e. the range outside the claimed lower limit, and the instant micrometer range of the instant drug to overcome the rejections based on the Noyes-Whitney law."

[1]-2. Disclosure of Muller et al. as to particle size

[1]-2-1. The particle size in the present invention is clearly distinguished from the particle size intended by Muller et al. and there is no overlap

The Examiner says that the particle size disclosed in Muller et al. overlaps with that in the present invention, that is, the particle size: 1 μm in Muller et al. is included within the mean particle size " above 1 μm" in the present invention.

Fig.1 of Muller et al. shows the particle distribution of the product pulverized with Jet Mill, and it is assumed that the particles have a mean particle size of about 3 micron to about 5 micron. Besides, it is disclosed in Muller et al., col. 2, lines 37-39 as follows:

> "Although 100% of the particles are smaller than approx. 25μm, only 8% of the particles are in the range below 1,000nm, i.e. 92% are $>1\mu m$."

Accordingly, it is assumed that 50 % of the particles shown in Fig. 1 of Muller et al. have about 3 to 25 micron, and 92 % thereof are microparticles. However, Muller et al. did not intend to cover such particles, because according to the invention of Muller et al., the suspension of nanoparticles is to be used as an injection, and such particles having such a large particle size cannot be injected due to clogging of the blood vessel. Muller et al. clearly disclose as follows in col.1, lines 60-62:

"As a nanosuspension, the active compound can be injected without blockade of blood capillaries"

Moreover, it is defined in claim 1 of Muller et al. that "the proportion of particles larger than 5 μm in the total population being less than 0.1 %".

On the other hand, in Example 1 and Examples 3 to 12 of the present invention, the products were micronized with a Jet Mill. As is mentioned hereinabove, the particles prepared by a Jet Mill are not intended by Muller et al.

Thus, Muller et al. teach away from the particles of the present invention which are too large to be injected safely. The particles of 1 μm intended by Muller et al. are clearly distinguished from the microparticles of "above 1 μm" of the present invention, and both particles are never overlapping.

[1]-2-3 As to the amended claims

As explained above, in the proposed amended claims, the lower limit is now specified to be "1.2 micron" or "1.5 micron".

[1]-3 Summary of arguments against Muller et al.

(1) The rejection is based upon a misunderstanding of the Noyes-Whitney law. Based on the misunderstanding the rejection is incorrect, and is contrary to the opinion of the Board of Patent Appeals, and hence should be withdrawn.

(2) The Examiner also agrees that Noyes-Whitney law does not apply to every compound, which is conformable with the opinion of the Board of Patent Appeals.

(3) It has experimentally been proved by Sanjoba's Declaration submitted on Sept. 9, 2004 that AS-3201 is a hydrophobic drug, and hence, there is a "specific extraordinary circumstance" which AS-3201 is not conformable to Noyes-Whitney law. AS-3201 has also been experimentally proved to be hydrophobic by the experiments shown in Ohashi's Declaration (C).

(4) It was experimentally confirmed in Ohashi's Declaration (C) by comparing the dissolution rate of AS-3201 between tablets containing nanoparticles and those containing microparticles, wherein both tablets show substantially the same dissolution rate. That is, the experimental results of Ohashi's Declaration (C) proves that AS-3201 is not conformable to Noyes-Whitney law.

(5) With respect to the understanding of the Examiner as both inventions are overlapping in "1 micron" of the particle size, the Examiner views merely the superficial text of the disclosure but overlooks the important factor that "the product shall never cause clogging of the vein", from which understanding it must be concluded that the Muller et al. particles never overlap with the microparticles of the present invention.

(6) In the amended claims, the "lower limit" of the micronized particles of the present invention is specified to be "1.2 micron" or "1.5 micron" which will be well in conformity with the Examiner's suggestion in the former Office Action.

As to the primary Negoro et al. reference, the Applicant has already explained the distinctions of the present invention. Since the secondary Muller et al. reference do not teach or suggest the specific micronized particle of AS-3201, the present invention is respectfully submitted to be patentable over the cited combination of Negoro et al. and Muller et al.

C. Re: Rejections of claims 1-20 and 63-82 under 35 USC 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Arbuthnot et al (6,458,811)

This ground of rejection is respectfully traversed.

Re : Arbuthnot et al.

According to the file history of Arbuthnot et al. USP 6,458,811, the patentee appealed to the Board of Patent Appeals on November 1, 1999 and filed a response to an Office Action (dated Oct. 10, 2001) on April 9, 2002. A copy of the file wrapper is attached hereto as Appendix 2-1.

In page 8, lines 7-1 from the bottom of said Arbuthnot's Response (Appendix 2-1), it is argued as follows:

"In addition, Lieberman at page 110 states,

> Size reduction and scale-up problems in the pharmaceutical industry are very similar to those found in "heavy industry", and are more often solved empirically rather than through the theoretical route."

Against this argument, the Examiners in the Board of Appeals issued a decision as shown in the attached Appendix 2-2, wherein it is mentioned as follows (page 2, para. 2, lines 3-6):

> "Although prior art of record taught that size reduction in general is prima-facie obvious approach to increase dissolution rate but the selection of a particular range of particle size are more often solved empirically rather than through theoretical route."

It is respectfully submitted that the decision of Board of Patent Appeals in that case restrains Examiners in the Examining Division of the USPTO from making the types of assumptions upon which the instant rejection is based.

And if so, even though Noyes-Whitney law is mentioned, not only in Arbuthnot et al. but also in Muller et al., the patentability must be studied and determined in each case. That is, if there is a "specific extraordinary circumstance", it shall be determined that the invention shall be evaluated to be "unobvious" without taking into account of Noyes-Whitney law.

The Applicant has already explained in the response to the former Office Action that in the instant case, there is a "specific extraordinary circumstance" in which the product of the invention does not match the Noyes-Whitney law. It may be summarized as follows.

(1) The compounds disclosed in Arbuthnot et al. are clearly distinguished from AS-3201 in the chemical structure, utility thereof, solubility, and the specific dissolution properties. There is no common point between them.

(2) It is disclosed in Arbuthnot et al. that a certain compound was prepared in two lots, and according to the results shown in Table 6 and Table 8, it is shown that even though the products of two lots had almost the same surface area, they showed different dissolution rate. Thus, it will be assumed that the compounds disclosed in Arbuthnot et al. is not conformable to the Noyes-Whitney law.

(3) Accordingly, Arbuthnot et al. do not teach or suggest or provide any motivation to complete the present invention.

In addition, as mentioned hereinbefore, Mr. Ohashi's Declaration (C) proved that AS-3201 does, in fact, not match the Noyes-Whitney law.

Accordingly, even if the primary Negoro et al reference is combined with the secondary Arbuthnot et al reference, the present invention could never be suggested from these references.

D. Re: Rejections of new claims 89-91 under 35 USC 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Muller et al (5,858,410) or Arbuthnot et al (6,458,811) in further view of Schneider et al (5,356,636)

As to the new claims 89-91, the Examiner cited a new secondary Schneider et al. reference, but even if this reference is combined with other references, the present invention is not obvious as is explained below.

Firstly, the Examiner mentioned in the outstanding Final Office Action, page 9, last line as follows:

"The references do not teach the instant acid in the composition."

"The references" in the above sentence means Negoro et al., Muller et al. and Arbuthnot et al. references, and hence the Examiner understands that those prior arts do not teach the present invention as claimed in claims 89-91.

It is further mentioned in the outstanding Final Office Action, page 10, para. 4 as follows:

> "It is the examiner's position that determining if a compound is stable or unstable is a routine skill in the art. If applicant asserts that the instant acid provide unexpected stability than that taught in the prior art, the examiner suggests submitting a Roule 132 declaration demonstrating this."

Along with the Examiner's suggestion, at this time, a new declaration, Mr. Ohashi's Declaration (E) is submitted.

In Experiment 1 of this Declaration (E), a stability test was done as to the following test samples; a sample comprising AS-3201 alone and a sample comprising

AS-3201 and excipients (for distinguishing purpose, the former being indicated "Test Sample 1" and the latter being "Test Sample 2").

Test Sample 1: AS-3201 (mean particle size, 1.5 μm) alone was compressed to a tablet.

Test Sample 2: AS-3201 (mean particle size, 1.5 μm) was mixed with various excipients, and the mixture was compressed to a tablet.

Test Conditions: Open state, 50°C/75%RH for one month under open condition (without stopper)

As a result, Test Sample 1 (AS-3201 alone) had a content of Related Substances (%) being 0.2 % (= contents of degradation product) after one month, which was the same data before testing. This means that Test Sample 1 (AS-3201 alone) was enough stable. On the other hand, in Test Sample 2 (further comprising various excipients) colored (color change ΔE) and showed remarkably increased Related Substances. For example, the product containing sodium carboxymethyl starch (=Primojel) formed 7.8% of degradated substances, the product containing crospovidone(=Polyplasdone XL) formed 47.0% of degradated substances, the product containing Povidone (=PVP K-30) formed 11.1% of degradated substances. Besides, the product containing crosscarmellose sodium (=Ac-Di-Sol) showed significant color change (ΔE) of 6.4.

The above test results show that AS-3201 alone is very stable, but when it is contacted with pharmaceutically acceptable excipients, it become very unstable, which has never been predicted by any person skilled in the art. Neither Negoro et al. and other references nor Schneider et al. teach or even suggest such properties.

Furthermore, in Experiment 2 of Mr. Ohashi's Declaration (E), tablets containing an acid having a p Ka value being below 5.6, e.g. tartaric acid (p Ka=2.93) (Formulation A) and tablets containing no acid (Formulation 1) were prepared and subjected to a stability test under the same conditions as in Experiment 1. By said test, it was confirmed that the tablets containing an acid was very stable. For example, the tablets containing tartaric acid showed 0.8% of Degradation, but on the other hand, the tablets containing

no tartaric acid showed 14.1% of Degradation. Likewise, the tablets containing other acids (Formulations B-E) showed superior stability in comparison with the corresponding tablets containing no acids (Formulation 2-5), as shown in Table 2 of Mr. Ohashi's Declaration (E).

In summary, the Applicant has demonstrated the unexpected superiority of stability of the composition of claims 89-91 as kindly suggested by the Examiner.

In view of the foregoing, it is respectfully submitted that all rejection has been overcome. Favorable reconsideration and allowance is solicited.

IV. REQUEST FOR PERSONAL INTERVIEW

A personal interview is requested prior to issuance of a first Office Action.

Respectfully submitted,

Mamoru OHASHI et al.

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